Altered neuronal network and rescue in a human MECP2 duplication model.

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Public Summary:
This work described the generation of mini-brains or organoids derived from reprogrammed skin cells of people suffering the MECP2 duplication, a genetic rare but devastating neurological disorder with no cure. Using these mini-brains, we found several defects at the molecular and cellular levels, including alterations in network synchronization that might be responsible for a series of neurological problems. More exciting, we use these observations to screen about 40 epigenetic drugs and found one that could rescue or reverte all neuronal problems in patient cells.

Scientific Abstract:
Increased dosage of methyl-CpG-binding protein-2 (MeCP2) results in a dramatic neurodevelopmental phenotype with onset at birth. We generated induced pluripotent stem cells (iPSCs) from patients with the MECP2 duplication syndrome (MECP2dup), carrying different duplication sizes, to study the impact of increased MeCP2 dosage in human neurons. We show that cortical neurons derived from these different MECP2dup iPSC lines have increased synaptogenesis and dendritic complexity. In addition, using multi-electrodes arrays, we show that neuronal network synchronization was altered in MECP2dup-derived neurons. Given MeCP2 functions at the epigenetic level, we tested whether these alterations were reversible using a library of compounds with defined activity on epigenetic pathways. One histone deacetylase inhibitor, NCH-51, was validated as a potential clinical candidate. Interestingly, this compound has never been considered before as a therapeutic alternative for neurological disorders. Our model recapitulates early stages of the human MECP2 duplication syndrome and represents a promising cellular tool to facilitate therapeutic drug screening for severe neurodevelopmental disorders.Molecular Psychiatry advance online publication, 8 September 2015; doi:10.1038/mp.2015.128.